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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,669	04/30/2001	Philippe Marliere	205907USOPCT	9510

22850 7590 04/24/2007

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	04/24/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 04/24/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/830,669	MARLIERE ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-104 and 106-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *86-89 and 91-96* is/are allowed.

6)☒ Claim(s) *97-104 and 106-118* is/are rejected.

7)☒ Claim(s) *90* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/26/2007 has been entered.

Receipt is acknowledged of an amendment, filed 1/26/2007, in which claims 1-85, and 105 were canceled, and claims 103, 106, 108 were amended. Currently, claims 86-104 and 106-118 are pending and under consideration.

Any rejection of record in the previous office actions not addressed herein is withdrawn.

Specification

The abstract of the disclosure is objected to because it contains legal phraseology such as "said cells" (lines 3 and 5), "said proteins" (line 4), and "said methods" (line 4). Correction is required. See MPEP § 608.01(b). This is a new objection.

Claim Objections

Claim 90 objected to because of the following informalities: the commas should be revised to set off the parenthetical elements to improve the grammar of the claim. Appropriate correction is required. This is a new objection.

Claim 106 is objected to because of the following informalities: the hyphen between the words "on" and October should be deleted in part (c) of the claim to improve the grammar of the claim. Appropriate correction is required. This is a new objection.

Response to Arguments - Claim Objections

The previous objections of claims 106 and 108-118 have been withdrawn in view of Applicant's amendment to the claim in the reply filed 1/26/2007.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 97-104 and 106-118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection.

Claim 97 is vague and indefinite in that the metes and bounds of the term "said culturing" are unclear. The term is unclear in that claim 97 depends from claim 86, which includes a selection stop in a culture medium (i.e., culturing) in step (b) and a subsequent culturing step in step (c). Thus, it is unclear if the isolation of the cells from the culturing refers to the isolation of cells from step (b) or step (c) of claim 86. It would be remedial to amend the claim language to clearly indicate from which step the cells are isolated.

Claims 98-102 depend from claim 97 and are indefinite for the same reasons applied to claim 97.

Claim 100 recites the limitation "the aminoacyl-tRNA" in line 1. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the phrase to recite "an aminoacyl-tRNA."

Claims 101-102 depend from claim 100 and are indefinite for the same reasons applied to claim 100.

Claim 103 recites the limitation "said aminoacyl-tRNA synthetase" in line 7. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the claim to recite "said valyl-tRNA synthetase." Further, claim 103 is vague and indefinite in that the metes and bounds of the phrase "sequence of the corresponding wild-type gene" are unclear. The phrase is unclear in that the specification does not define the nature of the correspondence, and it is unclear whether the correspondence is direct (i.e., the sequence is the sequence of the wild-type gene) or whether the correspondence is indirect (e.g., the claims encompass homologs of the wild-type sequence). Accordingly, one would not be reasonably apprised of the metes and bounds of the claim. It would be remedial to amend the claim language to clearly indicate that that the sequence is "the sequence of the wild-type valyl-tRNA gene."

Claims 104, 106 and 107 depend from claim 103 and are indefinite for the same reasons applied to claim 103.

Claim 108 recites the limitation "the one unconventional amino acid" in line 1 of step (c). There is insufficient antecedent basis for this limitation in the claim. There is antecedent basis for the term "the at least one unconventional amino acid." Thus, it would be remedial to delete "of the" from the phrase "the at least of the one unconventional amino acid, such that the phrase reads "the at least one unconventional amino acid."

Claims 109-118 depend from claim 108 and are indefinite for the same reasons applied to claim 108.

Claim 109 is vague and indefinite in that the metes and bounds of the phrase "wherein said culture medium in (b) allows the growth of said cell contains said unconventional amino acid or a precursor thereof" are unclear. The phrase is unclear in that claim 109 depends from both claims 86 and 108, each of which are drawn to a step of culturing in step (b). Claim 86 includes a selection stop in a culture medium (i.e., culturing) in step (b). Claim 108 includes a step of culturing a cell selected by the method according to claim 97. Thus, it is unclear which culturing step is being further limited by claim 109. Moreover, the phrase "in (b) allows the growth of said cell contains said unconventional amino acid" is unclear. It is unclear if the medium or the cell contains the unconventional amino acid or precursor thereof.

Claim 114 is vague and indefinite in that the metes and bounds of the phrase "wherein the culture medium in (b)" are unclear. The phrase is unclear in that claim 114 depends from both claim 108 and 86, each of which are drawn to a step of culturing in step (b). Claim 86 includes a selection stop in a culture medium (i.e., culturing) in step (b). Claim 108 includes a step of culturing a cell selected by the method according to claim 97. Thus, it is unclear which culturing step is being further limited by claim 114.

Claim 116 is vague and indefinite in that the metes and bounds of the phrase "culture medium of step (b)" are unclear. The phrase is unclear in that claim 116 depends from both claim 108 and 86, each of which are drawn to a step of culturing in step (b). Claim 86 includes a selection stop in a culture medium (i.e., culturing) in step (b). Claim 108 includes a step of

culturing a cell selected by the method according to claim 97. Thus, it is unclear to which culturing step claim 116 refers.

Claim 117 depends from claim 116 and is indefinite for the same reasons applied to claim 116.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 103, 104 and 107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The grounds of this rejection have been changed in response to Applicants' amendment of the claims in the response filed on 1/26/2007.

The rejected claims are drawn to bacterial or yeast cells obtained by methods of selection wherein a missense mutation is incorporated into a an essential gene (required for growth of the host cell) at a target codon and the cell is grown under selective conditions wherein 1) the culture medium does not contain a nutrient that will compensate for the lack of a functional copy of the essential gene product, and 2) the culture medium contains an amino acid encoded by the target codon (prior to mutation). Further, the cell must comprise an valyl-tRNA synthetase which recognizes a given amino acid and which is capable of charging onto one of its associated tRNAs an unconventional amino acid or an amino acid other than said given amino acid, wherein the

gene encoding the aminoacyl-tRNA synthetase contains at least one mutation compared with the sequence of the corresponding wild-type gene. The rejected claims thus comprise a set of yeast and bacterial cells that encompass a mutation in a valyl-tRNA synthetase gene of any bacteria or yeast cell, where the mutated valyl-tRNA synthetase is capable of mischarging a tRNA in the cell and suppressing a missense mutation in an essential gene.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes *E. coli* strains deposited at the CNCM under the Nos. I-2025, I-2026, I-2027, I-2339, I-2340, and I-2341, also referred to as strains β5366, β8144, β8146, β5479, β5485, and β5486, respectively (e.g. pages 7-9). Strain I-2025 (β5366) does not meet the structural or functional limitations of the claims in that the strain is incapable of growing without thymine or thymidine due to the absence of a mutation in any gene capable of suppressing the missense mutation in the thyA gene (e.g. Example 1). Strains I-2026 and I-2027 contain the K277Q allele of the ValS gene (e.g. page 24, lines 23-25). Strain I-2339 contains the R223H allele of the ValS gene (e.g. page 8, lines 13-24). Strain I-2340 contains the V276A allele of the ValS gene (e.g. page 8, lines 25-34). Strain I-2341 contains the D230N allele of the ValS gene (e.g. page 9, lines 7-8). Thus, each of the strains described in the instant specification is a strain of *E. coli* with a missense mutation in the ValS gene. The specification does not describe mutations in any other *E. coli* aminoacyl-tRNA synthetase genes. The specification does not describe any mutations in an aminoacyl-tRNA synthetase gene of a cell

isolated from any other type of organism, either yeast or bacteria. Further, the instant specification and prior art do not clearly describe what mutations in what functional domains of different aminoacyl-tRNA proteins will allow the mutated aminoacyl-tRNA synthetase to function in the manner recited in the rejected claims.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of *E. coli* strains with missense mutations in the ValS gene. The results are not necessarily predictive of other mutations that will confer the claimed function in other bacterial or yeast species. There is no evidence of record to indicate that a representative number of bacterial and yeast valyl-tRNA synthetase genes were know in the art at the time the invention was made. Thus, it is impossible for one to extrapolate from the few examples described herein those isolated cells that would necessarily meet the structural/functional characteristics of the rejected claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the genetic modifications required to confer the claimed function, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement

that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Given the very large genus of yeast and bacterial cells encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to genetic modifications of valyl-tRNA synthetase that meet the functional limitations of the claims for a representative number of bacterial and yeast organisms, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of isolated cells. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 103, 104 and 107.

Claim 106 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new rejection.

Claim 106 is drawn to *E. coli* strains deposited at the Collection Nationale de Culture de Microorganismes (CNCM) in Paris, France.

The application discloses *E. coli* strains that are encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

It is unclear whether this biological material is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

In the instant case, the specification provides the reference to the deposit, including the accession number, date of deposit, the name of the depository, and the complete taxonomic description. However, the specification provides only a partial address for the depository (i.e., Paris, France). It would be remedial to amend the specification to include the complete address of the depository: Institut Pasteur 28, rue du Dr Roux 75724 Paris Cédex 15, France.

Upon review of the entire contents of the application, no evidence could be found to indicate that the deposit to the CNCM was made under the Budapest Treaty. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request or for the enforceable life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and the deposit will be replaced if it should ever become inviable.

It is noted that a statement by the attorney of record that all restrictions upon availability to the public will be irrevocable removed upon granting of the patent was received on 7/28/2003.

Response to Arguments/112 1st Rejection

With respect to the rejection of claims 103, 104 and 107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, Applicant's arguments filed 1/16/2007 have been fully considered but they are not persuasive.

The response asserts that the amendment to the claims has obviated the rejection. This is not found persuasive, because Applicant was not in possession of a representative number of bacterial and yeast cells encompassed by the claimed genus. The specification provides only *E. coli* cells with mutations in the valyl-tRNA synthetase gene. The specification does not describe cells with mutations in the valyl-tRNA synthetase gene of any yeast organism or other bacterial organisms. Further, there is no evidence of record to indicate that the sequences of valyl-tRNA synthetase genes of a representative number of bacterial and yeast species were available at the time the invention was made such that one could make a representative number of the claimed strains. Moreover, without the sequence information, it is unclear if the structural information obtained with the *E. coli* valyl-tRNA synthetase gene would be sufficient to provide a structural/functional correlation for one to envision those other bacterial and yeast strains that fall within the claimed genus.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

Claims 86-89 and 91-96 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

jad

CELINE QIAN, PH.D.
PRIMARY EXAMINER

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL

A declaration by applicant or assignee, or a statement by applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection or rejection based on a lack of availability of biological material. Such a declaration:

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address. (See 37 C.F.R. § 1.803).

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of the patent. (See 37 C.F.R. § 1.808(a)(2)).

5. States that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 122. (See 37 C.F.R. § 1.808(a)(1)).

6. States that the deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer. See 37 C.F.R. § 1.806).

7. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Alternatively, it may be averred that deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g., see 961 OG 21, 1977) and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.